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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/965,528	09/26/2001	Y. Tom Tang	PF-0701 USA	3765

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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/965,528	TANG ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11,12,30-35,42-45,71 and 108-113* is/are pending in the application.

4a) Of the above claim(s) *1,12,30,33,35,44,45 and 71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,31,32,34,42,43 and 108-113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/27/04 has been entered.

2. Claims 1, 11-12, 30-35, 42-45, 71 and 108-113 are pending.

3. Claims 1, 12, 30, 33, 35, 44, 45 and 71 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 11, 31-32, 34, 42, 43 and 108-113 are under examination.

5. 35 U.S.C. § 101 reads as follows:
"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

6. Claims 11, 31-32, 34, 42, 43 and 108-113 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility essentially for the same reasons set forth in the previous Office Action, mailed 3/24/03.

Applicant's arguments, filed 1/27/04, have been fully considered, but have not been found convincing.

Applicant argues a variety of uses of the claimed antibodies have been described including the use to purify a polypeptide having a sequence of SEQ ID NO: 16, diagnostic, to target delivery for a pharmaceutical agent to tissues, and for use as an antagonist.

Again, applicants' specification lack information regarding a correlative or causal relationship between the secreted polypeptide normal islet cells and the tumor islet cell. Furthermore, as indicated in the previous office action that Leiter et al (J Biol Chem 260:13013-13017, 1985) indicate that using Southern blot analysis of SEQ ID NO: 16 homolog, the gene detected in a pancreatic polypeptide-producing islet cell tumor was indistinguishable from that in normal human leukocytes. Therefore, it is unclear whether the one skilled in the art would be able to distinguish between the secreted polypeptide from islet cell, islet cell tumor and the normal human leukocytes or combination thereof in the diagnostic test.

Applicant argues in conjunction with law cases that a small degree of utility is sufficient to satisfy utility. Applicant contends that an invention does not lack utility merely because the particular enbodiment disclosed in the specification lacks perfection or performs crudely, nor is it

essential that the invention accomplish all of its intended functions. If an invention is only partially successful in achieving a useful result, a rejection of the invention based on lack of utility is not appropriate. Applicant asserts that the antibodies to SEQ ID NO: 16 may be used to specifically identify islet cells in a tissue. This specific identification aspect of the claimed antibodies has "real world" utility in a diagnostic assay to identify hyperplasia of islet cell.

However, since the polypeptide of SEQ ID NO: 16, which the claimed antibodies bind to, has 178 amino acids while Adrian et al antibody recognizes only 36 amino acid residues of human pancreatic polypeptide. Thus, employing the claimed antibody in a diagnostic assay for islet tumor cell as a marker is not substantial utility because SEQ ID NO:16 is different form the 36 amino acids pancreatic polypeptide (PP) taught by Adrian *et al*. Further, the antibody of Adrian et al only recognizes a secreted polypeptide of the human pancreatic polypeptide while the claimed antibodies recognized a full length polypeptide of 178 amino acids that includes a precursor motif. Further, the specification has not established a correlative relationship between the normal and tumor islet cells.

Applicant asserts that demonstration of increased numbers of cells secreting pancreatic polypeptide has been described as a characteristic of type II hyperplasia of pancreatic islets. Applicant contends that an increase in the number of islet cells secreting pancreatic polypeptide may be quantified using microscopic techniques or flow cytometry techniques employing an antibody to SEQ ID NO: 16. Applicant asserts it is not necessary for one skilled in the art to distinguish between polypeptide having an amino acid sequence of SEQ ID NO: 16 is from normal islet cell and tumor islet cells in a diagnostic assay. Applicant asserts that the claimed antibody to SEQ ID NO: 16 is used as the marker for islet cells and an antibody to pancreatic polypeptide is used as a marker for cell containing pancreatic polypeptide and the number of double positive cells is quantified using microscopic or flow cytomety techniques.

Again, Applicants base their utility argument based on a homology of the polypeptide of SEQ ID NO: 16 to other known proteins. In this case SEQ ID NO:16 is different form the pancreatic polypeptide (PP) taught by Adrian *et al* or the secreted pancreatic polypeptide because the secreted polypeptide is only 36 amino acids in length while the claimed antibody recognizes 178 amino acids in length which include a precursor sequence that will not be secreted or detected in the diagnostic assay.

Applicant asserts that the claimed antibodies to SEQ ID NO: 16 may be used in immunohistopathological preparations of a sample of tissue from a biopsy allowing for accurate diagnosis by visually confirming abnormal patterns of islet cells associated with islet cell hyperplasias, including tumor.

However, Leiter et al (J Biol Chem 260:13013-13017, 1985) indicate that using Southern blot analysis of SEQ ID NO: 42 homolog, the gene detected in a pancreatic polypeptide-producing islet cell tumor was indistinguishable from that in normal human leukocytes. Therefore, it is unclear how one skill in the art will be able to distinguish between tumor and non-tumor tissue using the claimed antibody.

Applicant submits in conjunction with Brenner et al that pairwise sequence comparison methods are capable of detecting almost all relationships between proteins whose sequence identities are greater than 30%. Applicant concluded that one skilled in the art would recognize that a functional assignment of EXCS based on the significant homology to pancreatic polypeptide is more likely than not true.

However, there is no unique and universal definition of "similarity". The sequence, structure and function of proteins can be combined in different ways. There are proteins with very different sequence fold similarly and perform similar function, proteins with very similar sequence fold up differently, or proteins with very similar functions but still very different structure. Certain positions in the amino acid sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. The rejection sets forth that among related polypeptides, structural similarity is not predictive of functional similarity. Therefore, functional relatedness is not credible in the face of evidence in the art that structurally related polypeptides are frequently dissimilar functionally.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 11, 31-32, 34, 42, 43 and 108-113 stand also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to used the claimed invention for the same reasons set forth in the previous Office Action, mailed 3/24/03.

9. Further, the specification does not reasonably provide enablement for a method of preparing the antibody comprising immunizing an animal with a polypeptide "having" an "immunogenic fragment" of SEQ ID NO: 16. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The term "having" is open-ended, it expand the amino acid fragments of SEQ ID NO: 16 to include additional non disclosed amino acids on either or both sides of N-terminal or C-terminal of the immunogenic fragments. The instant claim language appears to encompass fragments. Such a recitation does not require that the amino acid encode the full length sequence set forth in SEQ ID NO:16; but rather encompasses any amino acid sequence comprising either the full length of SEQ ID NO:16 or *any fragment*. However, the specification does not appear to have

provided sufficient guidance as to which subsequences of SEQ ID NO:16 would share the function as a marker for islet cells. Neither does the specification appear to have provided any working examples of any immunogenic fragments. Thus it would require undue experimentation of the skilled artisan to determine which fragments of SEQ ID NO:16 would have the function of the full length molecule, and in turn make antibodies to the amino acid fragments of SEQ ID NO:16.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. Claims 109 and 112 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method of preparing the antibody comprising immunizing an animal with a polypeptide having the amino acid sequence of SEQ ID NO: 16.

Applicant is not in possession of a method of preparing the antibody comprising immunizing an animal with a polypeptide "having" an "immunogenic fragment" of SEQ ID NO: 16.

Applicant has disclosed only amino acid of SEQ ID NO: 16; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons

of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 11, 42-43 and 108, are rejected under 35 U.S.C. 102(b) as being anticipated by Adrian *et al* (IDS Ref. A) as is evidenced by Bost *et al,* Bendayan, Applicant Amendment filed 1/27/04 on page 13, lines 5-8 and Leiter et al (J. Biol. Chem., 260:13013-13017, 1985).

Adrian *et al* teach rabbit antibody to human pancreatic polypeptide (see page 288, left column, 3rd paragraph in particular). Although Adrian et al do not teach specific amino acid sequence of SEQ ID NO: 16, the amino acid sequence of pancreatic polypeptide, binding to "SEQ ID NO: 16" is considered an inherent property of the reference antibodies. As is evidenced by the Amendment filed on 1/27/04 on page 13, lines 5-8 and Leiter et al that the polypeptide of Adrian et al has 36 amino acids and wherein Leiter *et al* discloses the amino acid sequence of a 36 amino acid human pancreatic polypeptide and 95 amino acid precursor. The 36 amino acid polypeptide taught by Leiter *et al* is 100% identical to amino acids 1-36 of SEQ ID NO:36 (see page 13015, under Fig 3). Given the high sequence homology/identity between Adrian et al polypeptide and claimed SEQ ID NO: 16, the reference antibody of Adrian et al would have the inherent property of binding SEQ ID NO: 16.

Further, as is evidenced by Bost *et al* that an antibody "cross-reacts", i.e. binds to more than one protein sequence, mean that "specifically bind" with both proteins and still specific. Bost et al (Immuno. Invest. 1988 ;17:577-586) describe antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4-6 residues were identical (see entire document, especially the Abstract and Discussion).

Similarly, Bendayan (J. Histochem. Cytochem. 1995, 43:881-886) characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin, and shows that although the antibody is highly specific, it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagons, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that "an antibody directed against such a sequence, although still yielding specific

labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph in particular).

Claims 42-43 are included because an antibody is the same antibody irrespective how it is made.

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not bind to the SEQ ID NO:16 recited in the claims. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 1/27/04, have been fully considered, but have not been found convincing.

Applicant submits that to anticipate a claim, each and every element of the claim must be described, either expressly or inherently, in a single prior art reference. Verdegaal Bros. v. Union Oil of California, 814 F.2d 628, 631 (Fed. Cir. 1987). Applicant contends that the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teaching of the prior art. Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). The prior inherent characteristic must be established as a certainty, probabilities are not sufficient. in re Oelrich, 666 F.2d 578, 581 (CCPA 1981). Applicant submits that Adrian et al. does not teach or suggest that the antibody described therein would necessarily or for certain bind specifically to a polypeptide comprising an amino acid sequence of SEQ ID NO: 16.

However, given the 100% sequence identity between the Adrian et al human pancreatic polypeptide and claimed polypeptide; the Adrian et al antibodies would have the inherent property of binding human pancreatic polypeptide of SEQ ID NO: 16 in the absence of objective evidence to the contrary.

Applicant submits that the human pancreatic polypeptide as disclosed by Adrian et al. does not have an amino acid sequence of SEQ ID NO: 16. SEQ ID N0: 16 has an amino acid sequence of 178 amino acids wherein the pancreatic polypeptide of Adrian et al. has 36 amino acids. Leiter et al., 1985, J Biol. Chem., 260:13013-13017, discloses the amino acid sequence of a 36 amino acid human pancreatic polypeptide and a 95 amino acid precursor polypeptide. Both of these sequence differ in size and amino acid composition from a polypeptide comprising SEQ ID NO: 16. The difference in size and amino acid sequence shows that there is no certainty that the antibody as described in Adrian would bind to a polypeptide comprising an amino acid sequence of SEQ ID NO: 16. Nothing in the Adrian reference necessarily suggests the disclosed antibodies specifically bind polypeptides having an amino acid sequence of SEQ ID NO: 16.

However, an antibody the recognizes the amino acids 1-36 of SEQ ID NO: 16 would specifically bind with SEQ ID NO:16 because it has been establish that antibody binding of each protein is due to the presence of a homologous sequence in each protein in which 4-6 residues.

Applicant submits that neither Bost et al. nor Bendayan et al. make clear that specifically binding SEQ ID NO: 16 is necessarily a property of the antibodies disclosed by Adrian et al. The references disclose the possibility that an antibody to some antigens may specifically bind two different proteins and describe epitopes that may give rise to cross-reactivity. The references are directed to antibodies to different polypeptides than that of a polypeptide comprising SEQ ID N0:16. These references do not necessarily show or certainly show that the crossreactivity is a property of the antibodies of Adrian et a1. The prior inherent characteristic must be established as a certainty, probabilities are not sufficient.

However, Applicant's argument attempts to limit the term "specifically binds" in a manner inconsistent with the well-known and art-recognized specificity of antibody interaction with epitopes defined by particular amino acid sequences. That an antibody "cross-reacts", i.e., binds to more than one protein sequence, does not mean that the antibody does not "specifically binds" with both proteins. For example, Bost et al. (Immunol. Invest. 1988; 17:577-586) describe antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4 of 6 residues were identical (see entire document, but especially the Abstract and Discussion). Antibodies which bound either the HIV or IL-2 derived sequence did not cross-react with irrelevant peptides (e.g., "Results, page 579). Therefore, an antibody that recognizes the human pancreatic polypeptide which has 100% sequence identity of claimed SEQ ID NO: 16 at amino acids 1-36. Therefore, Adrian et al antibodies would recognize claimed SEQ ID NO: 16.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 109 and 111-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adrian *et al* (IDS Ref. A) as is evidenced by Bost *et al,* Bendayan, Applicant's Amendment filed 1/27/04 on page 13, lines 5-8 and Leiter et al (J. Biol. Chem., 260:13013-13017, 1985) in view of Harlow (1989) (of record).

Adrian et al. and evidentiary references have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a method of making polyclonal/monoclonal antibody in claims 109 and 112 and a monoclonal antibody in claim 111.

Harlow *et al* teach a method of producing polyclonal antibody to any antigen (see entire document and page 96, in particular). Harlow *et al* further teach that for practical reasons, rabbits represent a good choice for the routine production of polyclonal sera since they are easy to keep and handle and antibody produced are well characterized and easily purified. In addition, Harlow et al teach a method of producing monoclonal antibodies comprising immunizing an animal (i.e. a mouse) with a protein or portion thereof (i.e. fragments), harvesting spleen cells from said animal, fusing said spleen cells with myeloma cell line, and culturing said fused cells (i.e hybridoma) under conditions that allow production of said antibody. Harlow et al further teach that the monoclonal antibodies stems from their specificity, homogeneity and ability to be produced in unlimited quantities (see pages 141-157 in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce both polyclonal and monoclonal antibody using the method taught by Harlow *et al* with the pancreatic polypeptide as taught by Adrian *et al.*

One ordinary skill in the art at the time the invention was made would have been motivated to make do so because Harlow *et al* teach rabbits represent a good choice for the routine production of polyclonal sera since they are easy to keep and handle and antibody produced are well characterized and easily purified. Harlow *et al* further teach a method of producing polyclonal antibody to any antigen (See page 96, in particular). Further, One ordinary skill in the art at the time the invention was made would have been motivated to make monoclonal antibody against pancreatic polypeptide because the monoclonal antibodies produced exhibit a high degree of specificity and great affinity as taught by Harlow et al.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 1/27/04, have been fully considered, but have not been found convincing.

Applicant argument is the same as under 102(b) rejection. Applicant argues against Adrian *et al* and the evidentiary references and state that Harlow does not remedy the shortcomings of Adrian et al. Examiner's rebuttal is the same as under 102 (b) and contrary to Applicant assertions Harlow teaches the how to make monoclonal/polyclonal antibody in claims 109 and 111-112 with the specific advantages.

15. Claim 31 rejected under 35 U.S.C. 103(a) as being unpatentable over Adrian *et al* (IDS Ref. A) as is evidenced by Bost *et al,* Bendayan, Applicant's Amendment filed 1/27/04 on page 13, lines 5-8 and Leiter et al (J. Biol. Chem., 260:13013-13017, 1985) in view of Harlow (1989) (of record) as applied to claims 109 and 111-112 above, and further in view of Owens *et al* (1994) (of record).

The teachings of Adrian *et al*, Harlow and the evidentiary references have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a chimeric antibody, a single chain antibody, a Fab fragment, a $F(ab')_2$ fragment or a humanized antibody in claim 31.

Owens *et al* teach the modification of murine antibodies such as a chimeric antibody, a single chain antibody, a Fab fragment, a $F(ab')_2$ fragment or a humanized antibody antibodies monoclonal antibody technology, chimeric, single chain, Fab fragments, and $F(ab')_2$. Owens *et al* further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications, and the chimeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement – dependent cytotoxcity (see the entire document).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody as taught by Harlow against the human pancreatic polypeptide taught by Adrian et al as chimeric, humanized antibody, Fab and $F(ab')_2$ fragments taught by the Owens *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the humanized antibodies are much less likely to induce an immune response and because the antibody fragments are the reagents of choice for some clinical applications and the chimaeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement-dependent cytotoxcity as taught by Owens *et al*.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore,

the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 1/27/04, have been fully considered, but have not been found convincing.

Applicant argument is the same as under 102(b) rejection. Applicant argues against Adrian *et al* and the evidentiary references and state that Owens et al does not remedy the shortcomings of Adrian et al. Examiner's rebuttal is the same as under 102 (b) and contrary to Applicant assertions Owen et al teaches the specific fragments in claim 31 with the specific advantages.

16. Claim 31 rejected under 35 U.S.C. 103(a) as being unpatentable over Adrian *et al* (IDS Ref. A) as is evidenced by Bost *et al,* Bendayan, Applicant's Amendment filed 1/27/04 on page 13, lines 5-8 and Leiter et al (J. Biol. Chem., 260:13013-13017, 1985) in view of Harlow (1989) (of record) as applied to claims 109 and 111-112 above, and further in view of Bird *et al* (1988). (1994) (of record).

The teachings of Adrian *et al,* Harlow and the evidentiary references, have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a single chain antibody in claim 31.

Bird *et al* teach a single chain antigen binding proteins composed of an antibody variable light –chain amino acid sequence (V_L) tethered to a variable heavy –chain sequence (V_H) by a designed peptide that links the carboxyle terminus of the V_L sequence to the amino terminus of the V_H sequence. Bird *et al* further teach that the single chain antibodies have significant advantages over monoclonal antibodies in a number of applications such as lower back ground in imaging applications since the single chain antibody lack the Fc portion (see the entire document and page 426, left column, 2nd paragraph in particlular)).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by Harlow against the human pancreatic polypeptide taught by Adrian et al as a single chain antibody as taught by the Bird *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because single chain antibodies have significant advantages over monoclonal antibodies in a number of applications such as lower back ground in imaging applications since the single chain antibody lack the Fc portion as taught by Bird *et al*.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the

invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 1/27/04, have been fully considered, but have not been found convincing.

Applicant argument is the same as under 102(b) rejection. Applicant argues against Adrian *et al* and the evidentiary references and state that Bird *et al* does not remedy the shortcomings of Adrian et al. Examiner's rebuttal is the same as under 102 (b) and contrary to Applicant assertions Bird *et al* teach the specific fragment in claim 31 with the specific advantages.

17. Claims 32, 34, 110 and 113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adrian *et al* (IDS Ref. A), as is evidenced by Bost *et al,* Bendayan, Applicant's Amendment filed 1/27/04 on page 13, lines 5-8 and Leiter et al (J. Biol. Chem., 260:13013-13017, 1985) in view of U.S. Patent No. 5,766,910.

Adrian *et al* reference and the evidentiary references have been discussed, supra. Adrian et al further teach that the release of pancreatic polypeptide from normal cells has been shown to be under cholinergic control and is inhibited by atropine, whereas the secretion of pancreatic polypeptide from a tumor may be expected to be autonomous (see page 287, right column, middle paragraph in particular). Adrian et al concluded Atropine suppression test can be useful in either confirming the presence of a tumor secreting pancreatic polypeptide or excluding it in patients with moderate elevations of circulating pancreatic polypeptide (see page 291 last paragraph in particular).

The claimed invention differs from the reference teaching only by the recitation of a composition comprising the antibody and a suitable carrier/acceptable excipient in claims 32, 110 and 113, a composition wherein the antibody is labeled in claim 34.

The '910 patent teaches the use of antibodies in detection can be in vitro as in a diagnostic assay of a sample obtained from a subject or in vivo. When administered in vivo, the antibodies can be administered as a pharmaceutical composition comprising the antibody and a pharmaceutically acceptable carrier. Immunological procedures useful for in vitro detection of a target a protein or peptide in a sample include immunoassays that employ a detectable antibody. Such immunoassays include serum diagnostic assays. An antibody can be labelled so as to be detectable using various methods. For example, a detectable marker can be directly or indirectly attached to the antibody. (column 12, lines 5-20 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to place the antibody to human pancreatic polypeptide taught by the Adrian et al reference in a composition with a pharmaceutically acceptable carrier taught by the '910 patent and further label the antibody taught by Adrian et al as taught by the '910 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such composition can be useful for in vitro detection of a target a protein or peptide in a sample include immunoassays that employ a detectable antibody. Such immunoassays include serum diagnostic assays as taught by the '910 patent and further labeled antibodies can be used as a detectable marker as taught by `910 patent. Such diagnostic assay can be used with Atropine suppression test to confirming the presence of a tumor secreting pancreatic polypeptide or excluding it in patients with moderate elevations of circulating pancreatic polypeptide as taught by Adrian et al.

Form the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 1/27/04, have been fully considered, but have not been found convincing.

Applicant argument is the same as under 102(b) rejection. Applicant argues against Adrian *et al* and the evidentiary references and state that the `910 patent does not remedy the shortcomings of Adrian et al. Examiner's rebuttal is the same as under 102 (b) and contrary to Applicant assertions the `910 patent teaches the composition comprising antibodies with the specific advantages.

18. Claims 11, 42-43, 111-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leiter *et al* (JBC 260:13013-13017, 1985, (of record)) in view of Alisa Campbell (General properties and applications of monoclonal antibodies, Elsevier Science Publishers, 1984, section 1.1).

Leiter *et al* teach a 36 amino acid human pancreatic polypeptide which has 100% sequence homology to amino acids 1-36 of claimed SEQ ID NO: 16, an icosapeptide which has 100% sequence identity to amino acids 148-171 of SEQ ID NO:16, and a heptopeptide which has 100% sequence identity to amino acids 172-178 of SEQ ID NO: 16 (see page 13015, figure 3).

The claimed invention differs from the reference teachings only by the recitation of an isolated antibody which specifically binds to a polypeptide comprising an amino acid sequence of SEQ ID NO:16 in claim 11; and a method of making a monoclonal antibody comprising immunizing an animal with a polypeptide having amino acid of SEQ ID NO:16 or an immunogenic fragment thereof in claim 112, where in the antibody is monoclonal in claim 111.

Campbell teaches that it is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (see page 3 figure 11.1 in particular). One field of research in which monoclonal antibodies may prove of particular value

is in the study of chromosomal proteins. The search for those chromosomal proteins which are responsible for determining cell phenotype has been particularly long and comparatively fruitless and monoclonal antibodies are ideal tools for the dissection of the complex mixture of proteins. As hybridoma production becomes a more routine laboratory technique (see page 29 and 30 under Basic research in particular).

Claims 42-43 are included because an antibody is the same antibody irrespective of how it is made.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to to make a monoclonal antibody as taught by Campbell against the polypeptides of SEQ ID NO: 16 taught by the Leiter *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because it was customary at the time the invention was made to make monoclonals against any new macromolecule as taught by Campbell.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. Claim 31 rejected under 35 U.S.C. 103(a) as being unpatentable over Leiter *et al* (JBC 260:13013-13017, 1985, (of record)) in view of Alisa Campbell (General properties and applications of monoclonal antibodies, Elsevier Science Publishers, 1984, section 1.1) as applied to claims 11, 42-43, 111-112 above, and further in view of Owens *et al* (1994) (of record).

The teachings of Leiter *et al*, Campbell have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a chimeric antibody, a single chain antibody, a Fab fragment, a $F(ab')_2$ fragment or a humanized antibody in claim 31.

Owens *et al* teach the modification of murine antibodies such as a chimeric antibody, a single chain antibody, a Fab fragment, a $F(ab')_2$ fragment or a humanized antibody antibodies monoclonal antibody technology, chimeric, single chain, Fab fragments, and $F(ab')_2$. Owens *et al* further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications, and the chimeric

antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement – dependent cytotoxcity (see the entire document).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody as taught by Campbell against the human pancreatic polypeptides taught by Leiter *et al* as chimeric, humanized antibody, Fab and $F(ab')_2$ fragments taught by the Owens *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the humanized antibodies are much less likely to induce an immune response and because the antibody fragments are the reagents of choice for some clinical applications and the chimaeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement-dependent cytotoxcity as taught by Owens *et al*.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. Claim 31 rejected under 35 U.S.C. 103(a) as being unpatentable over Leiter *et al* (JBC 260:13013-13017, 1985, (of record)) in view of Alisa Campbell (General properties and applications of monoclonal antibodies, Elsevier Science Publishers, 1984, section 1.1) as applied to claims 11, 42-43, 111-112 above, and further in view of Bird *et al* (1988). (1994) (of record).

The teachings of Leiter *et al,* and Campbell, have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a single chain antibody in claim 31.

Bird *et al* teach a single chain antigen binding proteins composed of an antibody variable light – chain amino acid sequence (V_L) tethered to a variable heavy –chain sequence (V_H) by a designed peptide that links the carboxyle terminus of the V_L sequence to the amino terminus of the V_H sequence. Bird *et al* further teach that the single chain antibodies have significant advantages over monoclonal antibodies in a number of applications such as lower back ground in imaging applications since the single chain antibody lack the Fc portion (see the entire document and page 426, left column, 2nd paragraph in particlular)).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by Campbell against the human pancreatic polypeptides taught by Leiter *et al* as a single chain antibody as taught by the Bird *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because single chain antibodies have significant advantages over monoclonal antibodies in a number of applications such as lower back ground in imaging applications since the single chain antibody lack the Fc portion as taught by Bird *et al*.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

21. Claims 108-109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leiter *et al* in view of in view of Alisa Campbell (General properties and applications of monoclonal antibodies, Elsevier Science Publishers, 1984, section 1.1) as applied to claims 11, 42-43, 111-112 above, and further in view of Harlow (1989).

The teachings of the Leiter *et al* and Campbell have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a polyclonal antibody in claim 108 and a method of preparing the antibody, the method comprising immunizing an animal with a polypeptide having the amino acid sequence of SEQ ID NO: 16 or an immunogenic fragments thereof.

Harlow *et al* teach a method of producing polyclonal antibody to any antigen (see entire document and page 96, in particular). Harlow *et al* further teach that for practical reasons, rabbits represent a good choice for the routine production of polyclonal sera since they are easy to keep and handle and antibody produced are well characterized and easily purified.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce polyclonal antibody using the method taught by Harlow *et al* with the polypeptides of SEQ ID NO: 16 as taught by Leiter *et al*.

One ordinary skill in the art at the time the invention was made would have been motivated to make polyclonal antibody to polypeptides of SEQ ID NO: 16 because Harlow *et al* teach rabbits represent a good choice for the routine production of polyclonal sera since they are easy to keep and handle and antibody produced are well characterized and easily purified. Harlow *et al* further teach a method of producing polyclonal antibody to any antigen (See page 96, in particular).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the

invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

22. Claims 32, 34, 110 and 113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leiter *et al* in view of in view of Alisa Campbell (General properties and applications of monoclonal antibodies, Elsevier Science Publishers, 1984, section 1.1) in view of U.S. Patent No. 5,766,910.

The teachings of Leiter *et al* and Campbell references have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a composition comprising the antibody and a suitable carrier/acceptable excipient in claims 32, 110 and 113, a composition wherein the antibody is labeled in claim 34.

The '910 patent teaches the use of antibodies in detection can be in vitro as in a diagnostic assay of a sample obtained from a subject or in vivo. When administered in vivo, the antibodies can be administered as a pharmaceutical composition comprising the antibody and a pharmaceutically acceptable carrier. Immunological procedures useful for in vitro detection of a target a protein or peptide in a sample include immunoassays that employ a detectable antibody. Such immunoassays include serum diagnostic assays. An antibody can be labelled so as to be detectable using various methods. For example, a detectable marker can be directly or indirectly attached to the antibody. (column 12, lines 5-20 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to place the antibody taugth by Campbell to human pancreatic polypeptides taught by the Leiter et al reference in a composition with a pharmaceutically acceptable carrier taught by the '910 patent and further label the antibody taught by Adrian et al as taught by the '910 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such composition can be useful for in vitro detection of a target a protein or peptide in a sample include immunoassays that employ a detectable antibody. Such immunoassays include serum diagnostic assays as taught by the '910 patent and further labeled antibodies can be used as a detectable marker as taught by `910 patent.

Form the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

23. No claim is allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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